



The 7th Edition of TNM for Lung and Pleural Tumours

Akciğer ve Plevra Tümörlerin 7. TNM Sınıflandırması

TNM for Lung and Pleural Tumours

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Özet

Bu çalışmada, TNM sınıflandırmasının tarihi gelişimi ve TNM sınıflandırmasının son şeklinin oluşturulması konu edilmiştir. Ayrıca Küçük Hücreli Akciğer Kanseri de 7 TNM sınıflandırmasının kullanılması önerilmektedir. Böylece bir süre sonra bu konuda da yeni sınıflandırma çalışmalarına eklenebilecektir.

Anahtar Kelimeler

Akciğer Kanseri; Plevra Kanseri; TNM

Abstract

In this Study, the historical development of TNM classification and the forming process of final edition of TNM is mentioned. Besides, the use of TNM for small cell lung cancer cases is strongly encouraged in the 7th edition of TNM, and it allows for proposals for new classification to be trialed for a period to assess whether they should be incorporated into future editions.

Keywords

Lung Cancer; Pleural Cancer; TNM

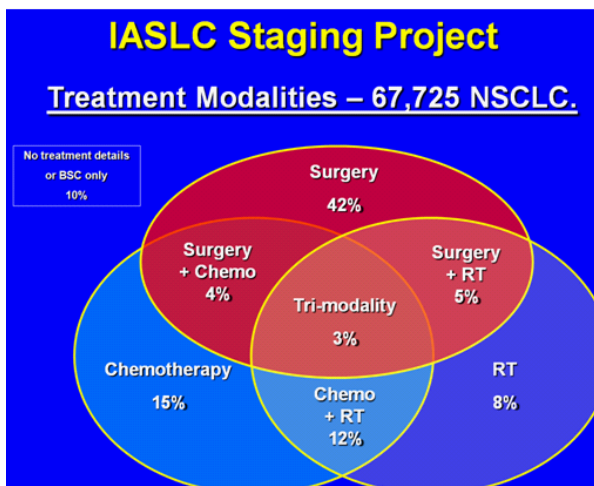
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The Process of Change

The TNM Classification is administered by 2 non-governmental organisations; the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). These 2 bodies conduct periodic revisions of the classification for all organ sites, most recently at a 7-year interval, and liaise to reduce any differences in the manuals each publishes. Closer cooperation in recent years has considerably improved consistency but there remain small differences in the classification in some organ sites.

For lung cancer all previous revisions had been informed by a reiterative analysis of the data base collected by Dr. Clifton Mountain at the M.D. Anderson Cancer Centre in the USA. This pioneering surgeon was the first to bring data-driven changes to the TNM classification for lung cancer [5]. However, over the intervening years his data base was seen to become increasingly unsatisfactory. This single centre data base did not allow for external valida-



Şekil 1. IASLC Staging Project

tion, and even at the last analysis in 1997 [6], consisted of just over 5,000 cases, too few to validate the large number of descriptors within the TNM classification. The cases were predominately surgical candidates. As a result, the TNM classification was coming under increasing criticism. Were the descriptors appropriate, was the classification relevant globally and appropriate for those bulkier tumours treated by non-surgical modalities?

In 1998 the International Association for the Study of Lung Cancer (IASLC) was convinced that it should develop a role in future revisions and established its Lung Cancer Staging Project [7]. It established an International database in collaboration with Cancer Research And Biostatistics (CRAB), a not-for-profit organisation based in Seattle, USA. Forty-six data sources in over 20 countries around the globe contributed over 100,000 cases to this data base. After an initial sift 81,495 cases has adequate data to be included in an analysis, 68,463 cases of non-small cell lung cancer and 13,032 cases of small-cell lung cancer (SCLC). Approximately half of these cases had undergone surgery as part of their treatment, around one third had received chemotherapy and one quarter radiotherapy (Figure 1). The analysis of this huge number of cases was conducted by CRAB and supervised by a number of sub-committees tasked with formulating recommendations on the T [8], N [9] and M [10] descriptors and the role of

TNM in SCLC [11-12]. All such recommendations were overseen by a Validation and Methodology sub-committee who established strict criteria for internal and external validation [13]. Once the T, N and M descriptors had been defined the resultant TNM stage groups were established using Recursive Partitioning and Amalgamation statistical methods [14]. The recommendations of the IASLC were submitted to the UICC and AJCC and after internal review, were accepted without change for the 7th edition of TNM for lung cancer.

The 7th edition.

Changes to the T descriptors are:

- Subclassify:
 - T1 as
 - T1a (≤ 2 cm) or
 - T1b (> 2 cm to ≤ 3 cm); and
 - T2 as
 - T2a (> 3 to ≤ 5 cm or T2 by other factor and ≤ 5 cm) or
 - T2b (> 5 to ≤ 7 cm).
 - Reclassify T2 tumours > 7 cm as T3.
 - Reclassify T4 tumours by additional nodule/s in the lung (primary lobe) as T3.
 - Reclassify M1 by additional nodule/s in the ipsilateral lung (different lobe) as T4.
 - Reclassify pleural dissemination (malignant pleural or pericardial effusions, pleural nodules) as M1.
- There were no changes to the N descriptors which, for the first time, have been validated in an International data base of patients treated with all modalities of care.

Changes to the M descriptors are:

- Reclassify pleural dissemination (malignant pleural effusions, pleural nodules) from T4 to M1a.
 - Subclassify M1 by additional nodules in the contralateral lung as M1a.
 - Subclassify M1 by distant metastases (outside the lung/pleura) as M1b.
- The full list of TNM descriptors in the 7th edition are shown in Table 1.

Additional recommendations.

In its analysis of the 13,032 cases of SCLC, the largest data base of its kind in the literature, the IASLC Staging Project confirmed the value of TNM in the clinical staging of small-cell lung cancer [11]. The use of TNM for SCLC cases is strongly encouraged in the 7th edition of TNM, especially for stratification in trials of chemo/radiotherapy in limited disease and for those cases treated by surgery. The data base also contained around 600 cases of carcinoid tumours. The analysis of these cases has shown that TNM has prognostic power in this tumour type [15]. As a result carcinoid tumours of the lung and tracheobronchial tree are now, for the first time, included in the 7th edition of TNM. Analysis of the N descriptors sub-committee was hampered by a lack of uniformity in the nomenclature of the regional lymph nodes. The IASLC Staging Project sought international agreement on a new Nodal Chart which, for the first time, has reconciled the Japanese “Naruke” and US “Mountain/Dressler” Nodal Charts and allowed the development of agreed definitions for the anatomical boundaries of each nodal station [16]. The UICC and AJCC have now recognised this chart and the associated definitions as the “recommended means of describing regional lymph node involvement for lung cancer”. This development has allowed for the reintroduction of minimum number of lymph nodes to be removed and examined histologically prior to assigning a pN category. The 7th edition recommends that “6 nodes/nodal stations should be removed/sampled for histological examination. These should include 3 nodes/stations from the mediastinum, one of which should be sub-carinal node #7, and 3

Table 1.**T – Primary Tumour**

TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1a	Tumour 2 cm or less in greatest dimension ¹
T1b	Tumour more than 2 cm but not more than 3 cm in greatest dimension
T2	Tumour more than 3 cm but not more than 7 cm; or tumour with any of the following features ² : • Involves main bronchus, 2 cm or more distal to the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumour more than 3 cm but not more than 5 cm in greatest dimension
T2b	Tumour more than 5 cm but not more than 7 cm in greatest dimension
T3	Tumour more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina ¹ but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe as the primary.
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary.

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M – Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion ³
M1b	Distant metastasis

Notes:

- The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.
- T2 tumours with these features are classified T2a if 5 cm or less or if size cannot be determined, and T2b if greater than 5 cm but not larger than 7 cm.
- Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

The resultant TNM stage groupings are summarised as:

Occult Carcinoma	TX N0 M0
Stage 0	Tis N0 M0
Stage IA	T1a N0 M0 T1b N0 M0
Stage IB	T2a N0 M0
Stage IIA	T1a N1 M0 T1b N1 M0 T2a N1 M0 T2b N0 M0
Stage IIB	T2b N1 M0 T3 N0 M0
Stage IIIA	T1a N2 M0 T1b N2 M0 T2a N2 M0 T2b N2 M0 T3 N1 M0 T3 N2 M0
Stage IIIB	T4 N0 M0 T4 N1 M0 T4 N2 M0
Stage IV	Any T N3 M0 Any T Any N M1a Any T Any N M1b

nodes/stations from the hilum or other N1 locations”.

“Visceral pleural invasion” has been a T2 descriptor since the early 1980s. However, there was no agreed definition of this feature. The pathologists within our committee reviewed the available literature and have developed a precise definition of “visceral pleural invasion”; i.e. “invasion beyond the elastic layer, including invasion to the visceral pleural surface” [17]. The use of elastic stains is recommended when this feature is not clear on routine histology.

Proposals for Testing.

The TNM classification allows for proposals for new classification to be trialled for a period to assess whether they should be incorporated into future editions. The IASLC Staging Project developed a number of such proposals. It is hoped that clinicians, radiologists and pathologists will collect data on these features to allow future analysis. These include:

a) Imaging evidence of lymphangitis carcinomatosa is usually a contraindication to surgical treatment. The “L” category which is used to assess “lymphatic invasion” is therefore not applicable. The radiological extent of lymphangitis is thought to be of prognostic importance. An exploratory analysis of this feature is proposed using a “cLy” category in which cLy0 indicates that radiological evidence of lymphangitis is absent, cLy1 indicates lymphangitis is present and confined to the area around the primary tumour, cLy2 indicated lymphangitis at a distance from the primary tumour but confined to the lobe of the primary, cLy3 indicates lymphangitis in other ipsilateral lobes and cLy4 indicates lymphangitis affecting the contralateral lung.

b) Concerns have been expressed that the definition of complete resection conferring R0 status is too imprecise and that

the application of General Rule 4 does not allow one to assess several features which may represent minimal residual disease and have an adverse prognostic influence. The category “Uncertain Resection” has been proposed [18] for testing. There is extant a category “R1(is)” which is applicable when the requirements for R0 have been met, but in situ carcinoma is found at the bronchial resection margin. Similarly category “R1(cy+)” is appropriate when the requirements for R0 have been met, but Pleural Lavage Cytology (PLC) is positive for malignant cells (v.i.). The wider use of these descriptors is encouraged to facilitate data collection and to assess the prognostic impact of these features following resection. A new category, “R0(un)”, is proposed to document those other features that fall within the proposed category of “Uncertain Resection”, i.e. No macroscopic or microscopic evidence of residual disease but any of the following reservations applies:

- i) Nodal assessment has been based on less than the number of nodes/stations recommended for complete resection.
- ii) The highest mediastinal node removed/sampled is positive.

c) A recent meta-analysis [19] has confirmed that pleural lavage cytology (PLC), undertaken immediately on thoracotomy and shown to be positive for cancer cells, has an adverse and independent prognostic impact following complete resection. Such patients may be candidates for adjuvant chemotherapy. Surgeons and pathologists are encouraged to undertake this simple addition to intra-operative staging and collect data on PLC+ve and PLC-ve cases. Where the resection fulfils all of the requirements for classification as a Complete Resection, R0 but PLC has been performed and is positive the resection should be classified as R1(cy+).

d) A standardized definition of visceral pleural invasion (VPI) has been incorporated into the 7th edition of TNM and recommendations included on the use of elastic stains in the determination of VPI [17]. It is important that data be collected using this definition so that the utility of this pT2 descriptor can be assessed more accurately in future revisions. A sub-classification has been proposed based upon a system published by the Japan Lung Cancer Society [20] and by Hammar [21]. It is proposed that the PL category be used to describe the pathological extent of pleural invasion:

- PL0 tumour within the subpleural lung parenchyma or invades superficially into the pleural connective tissue beneath the elastic layer*
- PL1 tumour invades beyond the elastic layer
- PL2 tumour invades to the pleural surface
- PL3 tumour invades into any component of the parietal pleura.

* Note:

In the TNM 7th edition PL0 is not regarded as a T descriptor and the T category should be assigned on other features. PL1 or PL2 indicate “visceral pleural invasion” i.e. T2a. PL3 indicates invasion of the parietal pleura, i.e. T3.

It is recommended that pathologists prospectively collect data based upon these sub-categories to facilitate future revisions of TNM.

e) There are suggestions that the depth of chest wall invasion may influence prognosis following resection of lung cancer. A sub-classification has been proposed, based upon the histo-

pathological findings of the resection specimen, dividing such pT3 tumours into pT3a if invasion is limited to the parietal pleura (PL 3), pT3b if invasion involves the endothoracic fascia, and pT3c if invasion involves the rib or soft tissue. Pathologists are encouraged to collect this information prospectively to facilitate analysis and future revisions.

f) The IASLC nodal chart has been adopted as the new international chart for the documentation of nodal stations at clinical or pathological staging where detailed assessment of nodes has been made, usually by invasive techniques or at thoracotomy [16]. The concept of nodal zones has been suggested as a simpler, more utilitarian system for clinical staging where surgical exploration of lymph nodes has not been performed [16]. An exploratory analysis suggested that nodal extent could be grouped into 3 categories with differing prognoses: i) involvement of a single N1 zone, designated as N1a, ii) involvement of more than one N1 zone, designated as N1b, or a single N2 zone, designated as N2a, and iii) involvement of more than one N2 zone, designated as N2b. It is suggested that radiologists, clinicians and oncologists use the classification prospectively, where more detailed data on nodal stations is not available, to assess the utility of such a classification for future revision.

g) The designation of additional tumour nodules of similar histological appearance in the lung(s) has been re-classified in the 7th edition of TNM. The UICC cannot determine that this is valid for cases in which multiple deposits are encountered and prospective data collection is necessary to fully validate this re-classification. It is recommended that radiologists, oncologists, surgeons and pathologists document in their clinical and pathological staging the number of nodules in the lobe of the primary, other ipsilateral lobes and the contralateral lung and the diameter of the largest deposit in each location. When found in the lobe of the primary, T3 disease, the size of the closest nodule from the primary tumour and its distance from the primary tumour should also be documented.

h) All cases in which there is metastatic spread to distant organs are classified as M1b disease. However, there are clear differences in prognosis based upon tumour burden and the critical nature of some organ sites. Such differences will influence the choice of treatment and the intent of treatment by all modalities of care. Selected patients with isolated metastases to a single organ may benefit from surgical treatment. Clinicians, oncologists and surgeons are encouraged to fully document the extent of disease in M1b cases, collecting data on all of the sites of (suspected) metastatic disease and whether such organs contain single or multiple deposits.

i) Carcinoid tumours are included within the 7th edition of TNM. This validates its use by surgeons and pathologists over several decades. However, further details are needed to assess the prognostic impact of certain features in carcinoid tumours (15); Typical versus atypical features, T size cut points, the prognostic impact of multiple deposits and whether these are associated with the syndrome of Diffuse Idiopathic Neuroendocrine Cell Hyperplasia (DIPNECH). In addition, in carcinoid tumours, in which long-term survival can be expected even when associated with multiple tumour nodules or nodal disease, it is important to collect data on disease specific survival.

j) PET scanning using FDG is now widely utilized and has had an impact of the accuracy of clinical staging and referrals for surgical treatment. In addition, a meta-analysis has shown that PET features, such as the maximum value of the Standardized Uptake Value (SUVmax) in the primary tumour prior to treatment is an independent prognostic factor [22]. Nuclear medicine specialists, clinicians and oncologists are encouraged to document the use of PET in clinical staging of lung cancer, and to record features such as SUV(max) in the primary and any nodal and/or metastatic sites.

k) We have reviewed the value of additional prognostic factors and summarised the present position regarding biological markers in lung cancer as prognostic factors [23, 24].

What has been retained from previous editions?

The value of certain descriptors used in previous editions of TNM could not be assessed by the data within our retrospective data base. In some cases this was for lack of any uniform definition, such as visceral pleural invasion or nodal designation, in others the descriptors were not recorded. Whilst this may indicate that colleagues had found the particular feature to lack any clinical utility, such as the extent of atelectasis or obstructive pneumonitis, without data we could not prove that the descriptor was obsolete.

The next phase of the IASLC Staging Project is to develop a prospective data base [25]. This will allow us to correct the geographical and treatment-related biases in the retrospective data base and allow us to assess the utility of those features on which we lack data. This will also expand the scope of the study to include mesothelioma, neuroendocrine tumours and thymic tumours in our proposals for the 8th edition and beyond. Any Institution that wishes to contribute to this project need only email information@crab.org with "IASLC Staging Project" in the subject line to establish a dialogue with our data centre.

How can we learn more about the 7th Edition of TNM in Lung and Pleural Tumours?

The IASLC has produced the first site-specific guidance on the 7th edition of TNM in thoracic oncology and a wide range of educational products, including aide memoirs cards and posters, a CD-Rom and web-based learning products. The IASLC Staging Handbook in Thoracic Oncology [26] is a pocket-sized book containing all of the fundamentals of the 7th edition and a number of illustrations, some in colour. The IASLC Staging Manual in Thoracic Oncology [27] is a more comprehensive book containing additional background material and a wider range of illustrations, all in colour. These include a TNM atlas illustrating the descriptors and a CT Atlas showing the precise anatomical position of the nodal stations and zones which are now the recommended means of describing regional node involvement in lung cancer. Anyone wishing to view these products is directed to the IASLC website at www.iaslc.org The educational products are available in a wide range of languages, including Turkish.

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